

# Uremic pruritus

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## CASE PRESENTATION

A 51-year-old African American male with diabetes, hypertension, and stage 5 chronic kidney disease presents with intense generalized itching of 1-month duration as well as nausea and vomiting of 3 days duration. He had no skin lesions that preceded the onset of itching. The patient described the itching as predominantly occurring during the day. He denied any occupational exposure. His past medical history was notable also for hepatitis C. His medications included aspirin, neutral protamine hagedorn insulin, calcitriol, calcium acetate, nifedipine, clonidine, lisinopril, and furosemide. He had been on these medications for more than 1 year at varying doses. Social history was significant for occasional tobacco and alcohol use as well as crack-cocaine consumption once every 4–6 weeks. There was no significant family history. Pertinent in the review of systems was the absence of a history of fever, weight loss, fatigue, or malaise. There was no history of jaundice. He denied oral or genital ulcers.

Blood pressure at presentation was 158/92 mm Hg and heart rate 80 beats/min. He was afebrile and had a normal respiratory rate. The patient had powdery deposits on his face. He was anicteric. He had bilateral pedal pitting edema. Examination of skin revealed generalized xerosis with multiple lichenified patches on the back, chest, abdomen, upper and lower extremities with more than 90% body surface involved. There were multiple excoriated 2–4 mm nodules on the lower extremities bilaterally (Figure 1a) and on the back (Figure 1b). There were no burrows or vesicles between his finger or toe web spaces. The oral cavity and genitalia were normal. The rest of the examination was unremarkable.

Blood work on admission revealed serum electrolytes within the normal range. Blood urea nitrogen, 93 mg/dl (normal range 8–18 mg/dl); serum creatinine, 10.8 mg/dl;

blood glucose, 155 mg/dl; liver function tests including transaminases and bilirubin were within normal limits; serum albumin, 3.6 g/dl (normal range 3–5 g/dl); serum calcium, 7.7 mg/dl; serum phosphate, 4.4 mg/dl; intact-parathyroid hormone (iPTH), 266 pg/ml. White blood cell count was  $9.58 \times 10^6/l$  (normal range  $4.5\text{--}11 \times 10^6/l$ ), white blood cell count differential: segmented neutrophils 54% (normal range 54–62%), lymphocytes 15.9% (normal range 25–33%), and monocytes 5.8% (normal range 3–7%), eosinophils 24% and less than 5% band forms. Peripheral smear examination revealed anisomicrocytosis with burr cells and spherocytes. Antinuclear antibody was negative. Thyrotropic hormone was 2.38 mU/ml.

## SKIN BIOPSY FINDINGS

A punch-skin biopsy from the left thigh was performed. The biopsy revealed perivascular inflammation with eosinophils, dermal hemorrhage, and psoriasiform hyperplasia with spongiosis, rare apoptotic keratinocytes and parakeratosis. A Periodic acid-Schiff digested stain was negative for fungal elements and a Congo red stain was negative for amyloid (Figure 2a and b).

## FINAL DIAGNOSIS

Uremic pruritus.

## FOLLOW UP

Given the typical histological findings from the skin biopsy in the setting of advanced renal failure, a diagnosis of uremic pruritus was made. Other possibilities that are associated with itching in end-stage renal disease patients were also considered in the differential diagnosis (Table 1). Drug-induced hypersensitivity was a possibility; however, the patient had not been treated with any new medication. The eosinophilia was most probably from the uremic pruritus state, as mast cells and histamine release is implicated in the pathogenesis (as discussed below). The PTH level was within the range recommended by Kidney Disease Outcomes Quality Initiative guidelines. Furthermore, there was no significant interval change that could have plausibly explained the abrupt onset of itching. The absence of jaundice and the normal liver function tests ruled out the possibility of cholestatic hepatitis. The patient was initiated on dialysis. He

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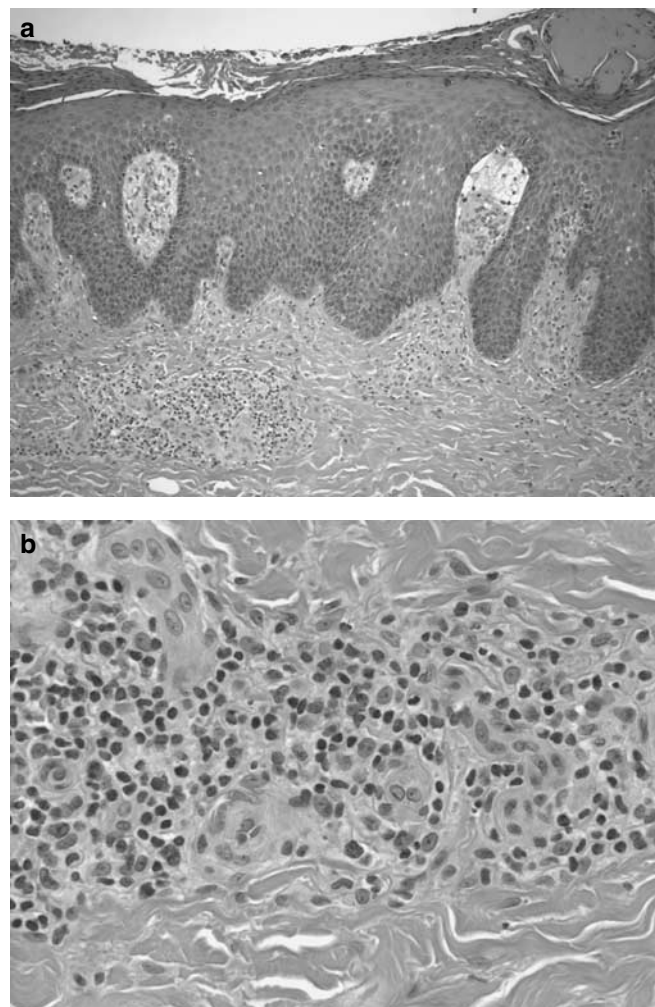
**Figure 1 | Examination of skin.** (a) Intense skin rash on the lower extremity. (b) Intense skin rash on the back.

was also treated with topical corticosteroids (1% hydrocortisone) and an anti-itch ointment containing 0.5% each of camphor and menthol in an emollient base. After 3 weeks of dialysis, his pruritus had substantially improved. The skin lesions improved with a short course of the topical agents and adequate dialysis treatment (urea reduction ratio 76%).

## DISCUSSION

### Uremic pruritus

Itching in patients with advanced kidney failure or among patients on dialysis can be quite disabling – affecting sleep, interfering with work, and potentially compromising quality of life.<sup>1</sup> The itching may be either generalized or localized. The prevalence of uremic itching reported in the literature ranges between 50 and 90%.<sup>2</sup> Risk factors include male gender, high levels of blood urea nitrogen, elevated calcium, phosphorus and  $\beta$ 2-microglobulin levels.<sup>1</sup> Despite advances in the care of end-stage renal disease (ESRD) patients, the management of pruritus remains one of the most challenging



**Figure 2 | Skin biopsy findings.** (a) Superficial perivascular lymphocytic infiltrate with eosinophils, dermal hemorrhage, and psoriasiform hyperplasia. Periodic acid-Schiff digested stain negative for fungal elements (original magnification  $\times 10$ ). (b) Superficial perivascular, predominantly lymphocytic infiltrate with eosinophils (original magnification  $\times 40$ ).

**Table 1 | Causes of itching in end-stage renal disease patients**

(1) <i>Uremia related</i>
(a) Uremic itching
(b) Xerosis
(c) Anemia of chronic kidney disease
(d) Secondary hyperparathyroidism
(2) <i>Uremia unrelated</i>
(a) Drug-induced hypersensitivity
(b) Senility
(c) Hepatitis
(d) Diabetes mellitus
(e) Hypothyroidism
(f) Iron-deficiency anemia
(g) Lymphoproliferative/solid tumors
(h) Hypercalcemic states

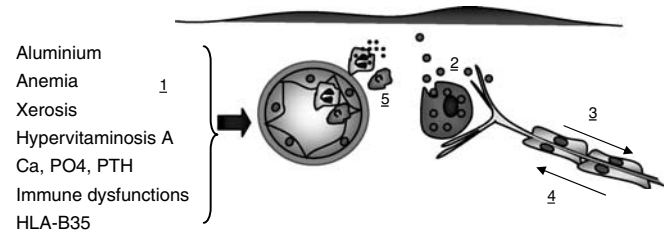
clinical problems for the treating nephrologist. Although the association of uremia with pruritus has been recognized for many years, the precise pathophysiologic mechanisms remain obscure.

### Pathogenesis of uremic pruritus

Nearly 40 years ago, Massry *et al.*<sup>3</sup> suggested a prominent role for secondary hyperparathyroidism and associated derangements of calcium and phosphorus metabolism in the pathogenesis of uremic pruritus. There are conflicting reports with respect to correlation of pruritus with elevated iPTH.<sup>4</sup> Although PTH itself is not pruritogenic when injected into the skin, elevated  $\text{Ca} \times \text{P}$  product is strongly correlated with pruritus. Apart from the above-described factors, possible roles for abnormal skin innervation, somatic neuropathy, elevated histamine levels, and opioid receptors have also been suggested (Figure 3).<sup>5</sup>

Neurophysiological factors are considered to play an important role in ESRD-associated pruritus. Pruritus is thought to originate in the terminal branching of afferent nonmyelinated C fibers distinct from those involved with pain that are located in the lower epidermis or dermal-epidermal junction. Mast cells in the dermis lie adjacent to afferent C neuron terminals and interactions between these structures play an important role in the mediation of pruritus.<sup>6</sup> Mast cells release several substances such as histamine, proteases, interleukin-2, and tumor necrosis factor. Histamine is a well-known pruritogen that directly stimulates the neurons terminals by H1 receptor. One study suggested abnormal sprouting of intraepidermal neuron-specific enolase – immunoreactive nerve fibers in uremic patients. This suggested abnormal pattern of cutaneous innervations as a presumptive cause for pruritus in ESRD patients.<sup>5</sup> It has also been observed that substance *P* stimulates  $\mu$ -opioid receptors in peripheral nerves and brain, and altered balance between  $\mu$ -opioid and  $\kappa$ -opioid stimulation leads to itching. The effects of  $\mu$ -opioid stimulation and substance *P* are countered by the stimulation of  $\kappa$ -opioid receptors by novel  $\kappa$ -opioid agonist, nalfurafine. These studies in animal models and subsequently in a subset of ESRD patient population have established a convincing role for  $\mu$ -opioid receptors in ESRD-associated pruritus.<sup>7</sup>

Several other factors are implicated in the pathogenesis of itching in uremic patients. Xerosis (dry skin) is very prevalent in ESRD patients.<sup>8</sup> Although association of xerosis with pruritus has been inconsistent, it may explain the higher prevalence of pruritus in elderly patients with ESRD. Additional factors that have been suggested as potential etiologies of pruritus in ESRD patients include high serum levels of magnesium, aluminum, and substance *P*; hypervitaminosis A and peripheral neuropathy. Anemia has also been suggested as an important predisposing factor, although definitive proof has been elusive.<sup>9</sup> More recently, with a substantial body of evidence accumulated in favor of the concept that the uremia is an inflammatory state, uremic pruritus is considered as a skin counterpart of chronic ongoing inflammation in these patients. Serum albumin was found to be lower in patients with severe pruritus in comparison to those without this symptom. Some studies have corroborated these findings and showed severity of pruritus correlates with poor survival and dialysis inade-



**Figure 3 | Working model for pathogenesis of uremic pruritus.**

(1) Several substances have been proposed to produce pruritogenic environment. (2) Histamine released from mast cells, in response to pruritogenic substances, stimulates C-terminal nerve endings. (3) A cascade of signals from nerve endings activate specific areas in the central nervous system resulting in perception of itch. (4) By a direct axon reflex mechanism, sensory nerve endings release neuropeptides. (5) Locally released neuropeptides aggravate the itch response by stimulating accumulation of inflammatory cells and release of pruritic mediators.

quacy.<sup>10</sup> The uremic inflammatory state also explains higher number of mast cells in dermis. However, a study which analyzed the number of dermal mast cells and serum levels of histamine did not show any correlation with the degree of pruritus.<sup>11</sup> Finally, a high prevalence of HLA-B35 reported in pruritic ESRD patients suggested genetic predisposition.

Regardless of the mechanism, the final common pathway appears to be the release of histamine from mast cells. This is supported by the observation that ultraviolet-B phototherapy reduced mast cell number and improved itching significantly, though there is no correlation between mast cell number and severity of pruritus in ESRD patients.<sup>11</sup>

### Diagnosis of uremic pruritus

Uremic pruritus is often considered a misnomer for the following reasons: pruritus in ESRD patients is not universal; it does not correlate with severity of uremia; even high-flux dialysis does not alleviate the problem; and pruritus is not seen in acute renal failure patients. A skin biopsy in patients with uremic pruritus is usually inconclusive. Repetitive scratching leads to excoriations, which in turn leads to superimposed dermatologic conditions, such as lichen simplex, prurigo modularis and keratotic papules (a perforating folliculitis), and follicular hyperkeratosis.<sup>12</sup> For epidemiological purposes, specific criteria are used to diagnose uremic pruritus (Table 2).

### Management

Renal transplantation remains the only current definitive treatment for severe refractory uremic pruritus in ESRD patients. However, this is frequently not feasible or may not be immediately possible. Therefore, a reasonable approach is to optimize the dialysis dose,<sup>1</sup> treat with erythropoietin<sup>9</sup> and iron supplementation, and treat secondary hyperparathyroidism with a view to maintaining the calcium and phosphate product at  $<55$ . Several treatment modalities have been tried in the treatment of uremic pruritus. However, the evidence for most of the therapies is based on uncontrolled trials or case series (Table 3).



**Table 2 | Criteria for the diagnosis of uremic pruritus<sup>20</sup>**

- 1 Pruritus appears shortly before the onset of dialysis, or at any time, without evidence of any other active disease that could explain the pruritus.
- 2 more than or equal to three episodes of itch during a period of <2 weeks, with the symptom appearing a few times a day, lasting at least few minutes, and troubling the patient.
- 3 Appearance of an itch in a regular pattern during a period of 6 months, but less frequently than listed above.

The most prevalent finding in uremic patients is xerosis. Evidence supports use of emollients, such as aqueous gel containing 80% water in the treatment of pruritus. In an uncontrolled study, 16 out of 21 patients studied had significant relief from symptoms, out of whom nine reported complete abolition of symptoms of pruritus.<sup>13</sup> Patients can be advised to use mild soaps and apply these moisturizing emollients atleast twice daily.

The role of UVB has been shown to be therapeutic in renal pruritus in double-blind trials.<sup>14</sup> It is considered as a safe and convenient therapy for uremic pruritus. The mechanism of the antipruritic effect of UVB is not completely understood. Among the proposed mechanisms are inactivation of a circulating pruritogenic substance, formation of a photo-product, which relieves pruritus, alteration of divalent ion content in the skin, and promotion of cutaneous-nerve degeneration.

Immune dysregulation and altered pattern of lymphokine production are considered to be major contributory factors for pruritus. Essential fatty acids such as  $\gamma$ -linolenic acid (GLA) reduce lymphocyte proliferation and lymphokine production and decrease severity of itching. A recently published prospective, randomized, double-blind, placebo-controlled, crossover study addressed this issue.<sup>15</sup> In this study, patients were randomly assigned to treatment with either 2.2% GLA cream or placebo-based cream applied three times a day for 2 weeks and then patients were crossed over to the opposite group. Severity of pruritus was evaluated by using a traditional visual analogue scale and a modified questionnaire method in 16 patients. There was a greater antipruritic effect of GLA and persistence of a residual effect into the second treatment period after GLA treatment. In another study, nine and seven patients were randomly assigned and treated with GLA-rich evening primrose oil or linoleic acid, respectively, for 6 weeks.<sup>16</sup> Uremic symptoms such as dryness, pruritus and erythema, and plasma concentrations of essential fatty acids were analyzed. The patients given oral GLA-rich evening primrose oil exhibited a significant improvement in skin scores and increase in precursors of anti-inflammatory prostaglandins with no concomitant alterations in proinflammatory prostaglandin precursors suggesting that it is a better supplemental source than linoleic acid alone in terms of shifting eicosanoid metabolism towards anti-inflammatory state.

Capsaicin 0.025% cream is another topical agent tried in the management of uremic pruritus.<sup>17</sup> Local application of capsaicin depletes the peripheral neurons of substance P and

**Table 3 | Therapeutic options in uremic patients**

- |                              |
|------------------------------|
| <i>Dialysis related</i>      |
| (a) Renal transplantation    |
| (b) Efficient dialysis       |
| (c) Erythropoietin           |
| <i>Topical treatment</i>     |
| (a) Skin emollients          |
| (b) Capsaicin                |
| (c) Topical steroids         |
| <i>Physical treatment</i>    |
| (a) Phototherapy             |
| (b) Acupuncture              |
| (c) Sauna                    |
| <i>Systemic treatment</i>    |
| (a) Low-protein diet         |
| (b) Primrose oil             |
| (c) Lidocaine and mexilitine |
| (d) Opioid antagonists       |
| (e) Activated charcoal       |
| (f) Cholestyramine           |
| (g) Serotonin antagonists    |
| (h) Parathyroidectomy        |
| (i) Thalidomide              |
| (j) Nicergoline              |
| (k) Nalfurafine              |

blocks the conduction of pain or pruritus. In this study, 14 out of 17 patients reported marked relief and five out of these 14 patients had complete remission of pruritus during capsaicin treatment. Capsaicin was significantly more effective than placebo with prolonged antipruritic effect up to 8 weeks post-treatment.

As imbalance in  $\mu$ - and  $\kappa$ -opioid stimulation has been implicated in the pathogenesis, manipulation of opioid system in the body has been attempted in the management of pruritus. Naltrexone, an opioid antagonist, is effective in a subset of patients with uremic pruritus.<sup>18</sup> However, in a placebo-controlled, double-blind crossover study of uremic patients with persistent, treatment-resistant pruritus, there was no significant difference between naltrexone and placebo.<sup>19</sup> Given this conflicting results and high incidence of gastro-intestinal adverse events, naltrexone is not considered a preferred drug in uremic pruritus. Nalfurafine, a new  $\kappa$ -opioid receptor agonist, was tried in the treatment of uremic pruritus. In a meta-analysis of two multicenter, randomized, double-blind, placebo-controlled studies on adult hemodialysis patients who had severe intractable pruritus, patients were randomized to receive nalfurafine 5  $\mu$ g or placebo intravenously three times a week, after each dialysis session for 2-4 weeks. Primary outcome measures decreased in worst itching visual analogue scale score. Secondary outcome measures were daytime itching intensity and sleep disturbances.<sup>7</sup> Significantly, more nalfurafine-treated patients responded within 2 weeks of run-in than placebo group (36 versus 14%). Drug-related side effects were comparable between the groups.

In summary, uremia remains the commonest cause of pruritus in ESRD patients, although it represents a diagnosis of exclusion. Uremic pruritus may have diverse skin manifestations and these frequently mimic a drug-induced hypersensitivity reaction. The early diagnosis and prompt treatment of uremic pruritus focuses on some general strategies that include the optimization of dialysis dose, erythropoietin, and management of secondary hyperparathyroidism. More specific treatments that appear promising but have not been proven to be definitively efficacious include UVB light, and the novel  $\kappa$ -opioid-agonist nalfurafine leads to significant improvement.

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